On the Effect of a Cation Binding Site in an Asymmetric Ligand for a Catalyzed Nucleophilic Substitution Reaction

Barry M. Trost* and Rumen Radinov

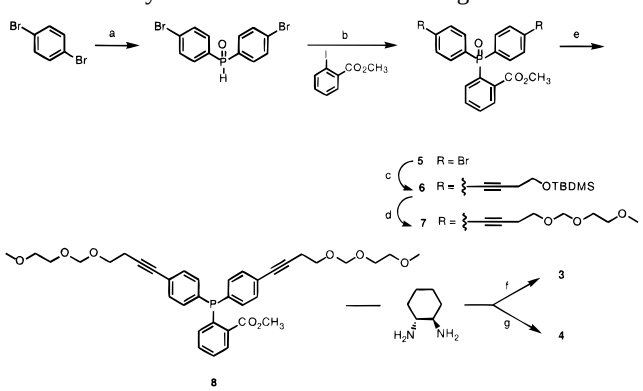
Department of Chemistry, Stanford University
Stanford, California 94305-5080

Received March 4, 1997

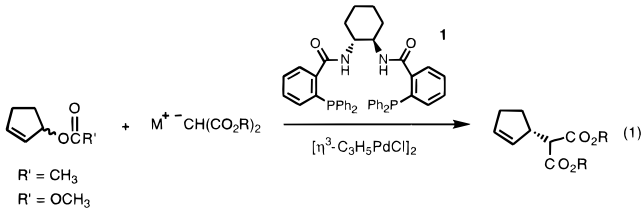
The development of an understanding of asymmetric induction in successful asymmetric catalytic reactions is important to establish a basis for the rational design of new asymmetric reactions. The complexity of the issues involved make such a task particularly challenging. Consider the use of asymmetric allylic alkylations catalyzed by palladium as illustrated in eq 1.[1] Four motifs have been put forward to explain asymmetric induction in such cases: (1) electronic desymmetrization of the intermediate π-allylpalladium complex as in cases wherein the binding atoms of the bidentate ligand are different,[2,3] (2) steric strain creating differential bonding between the two allylic termini and palladium,[4] (3) secondary interactions with the incoming nucleophile by asymmetric attachment of an ion binding group,[5] or (4) a chiral pocket.[6] For ligand **1** a model involving the concept of a "chiral pocket" has been proposed, but all attempts to obtain direct evidence such as X-ray crystallography or NMR spectroscopy have proven fruitless. While evidence disfavors electronic desymmetrization involving coordination of an amide and a phosphine,[7] metal ion coordination with the incoming nucleophile has some attractions. For example, there is a strong metal ion effect as shown by the fact that the enantiomeric excess (ee) increases in the order $Na^+ < K^+ < Rb^+ < Cs^+$.[8] However, since these results parallel a cation effect seen with tetraalkylammonium salts in the order $(CH_3)_4N^+ < (C_2H_5)_4N^+ < (n\text{-}C_4H_9)_4N^+ < (n\text{-}C_6H_{13})_4N^+$,[9] specific ion binding effects are difficult to discern. It is particularly noteworthy that, in this case, the escort ion, the cation, appears to play a much more significant role than the nucleophile, the anion, even though the latter actually binds to the allyl unit in the transition state of the enantiodiscriminating step.

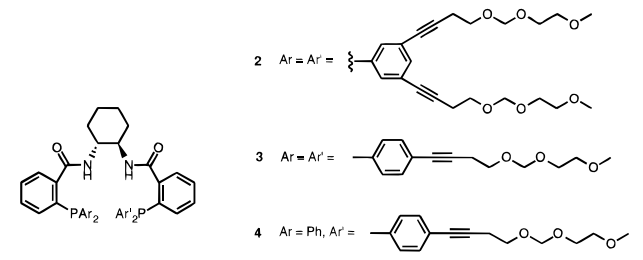
Much interest has focused on the design, synthesis, and study of synthetic ion channels to mimic natural transport proteins.[10] One can conceive superimposing such a concept onto the working model for the asymmetric induction of eq 1, which invokes a "chiral pocket." Modeling suggested that substituents attached to the phenyl rings of the diphenylphosphino moiety of **1** would project into the "chiral space" in which the reactants must reside. The unusual effects observed in eq 1 suggested that incorporating cation binding sites to transport the counterion of the nucleophile rather than the nucleophile itself may affect both enantioselectivity and rate. Simple glyme-like units, as depicted in ligands **2**−**4**, were chosen for synthetic simplicity and structural flexibility for the tentacle to reach out into solution to coordinate and then to fold inward to deliver the ion pair.

Scheme 1. Synthesis of Cation Channel Ligands[a]



[a] Key: (a) *n*-C_4H_9Li, ether, −75 °C, $(C_2H_5)_2NPCl_2$ then HCl, H_2O, $CHCl_3$, 43%; (b) $(Ph_3P)_4Pd$, *N*-methylmorpholine, $PhCH_3$, 120 °C, 69%; (c) HC≡$CCH_2CH_2OTBDMS$, $(Ph_3P)_4Pd$, CuBr, $(C_2H_5)_3N$, 70 °C; (d) TBAF, THF, 0 °C then MEM-Cl, $(i\text{-}C_3H_7)_2NC_2H_5$, CH_2Cl_2, room temperature (rt), 78% from **5**; (e) $HSiCl_3$, PhH, reflux, 47%; (f) $Ba(OH)_2$, H_2O, CH_3OH, rt, then HBTU, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C, 91%; (g) i. $Ba(OH)_2$, CH_3OH, rt then HBTU, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C; ii. 2-(diphenylphosphino)benzoic acid, HBTU, $(C_2H_5)_3N$. HBTU = *O*-(1H-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate.





Ligands **2** and **3** have formal C_2 symmetry; whereas, ligand **4** tests the importance of this symmetry element. Scheme 1, which outlines the synthesis of **3** and **4**, illustrates the facility by which such ligands are accessible. Ligand **2** was obtained analogously from 1,3,5-tribromobenzene.

The octopod ligand **2** proved unsuitable for allylic alkylations, presumably because of steric hindrance. On the other hand, the tetrapod ligand **3** and dipod ligand **4** generated active cata-

(1) For reviews, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. Heumann, A.; Reglier, M. *Tetrahedron* **1995**, *51*, 975. Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., VCH Publishers; Inc.: New York, 1993. Fiaud, J. C. In *Metal-Promoted Selectivity in Organic Synthesis*; Graziani, M., Hubert, A. J., Noels, A. F., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991. Consiglio, G.; Waymouth, R. M. *Chem. Ber.* **1989**, *89*, 257.

(2) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566. Dawson, G. J.; Frost, C. G.; Williams, J. M. J.; Coate, S. W. *Tetrahedron Lett.* **1993**, *34*, 3149. Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769. Baltzer, N.; Macko, L.; Schaffner, S.; Zehnder, M. *Helv. Chem. Acta* **1996**, *79*, 803.

(3) Knühl, G.; Sennhenn, P.; Helmchen, G. *Chem. Commun.* **1995**, 1845. Okada, Y.; Minami, T.; Umezu, Y.; Nishikawa, S.; Mori, R.; Nakayama, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 667.

(4) Mackenzie, P. B.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2046. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. von Matt, P.; Lloyd-Jones, G. C.; Minidis, A. B. E.; Pfaltz, A.; Macko, L.; Neuberger, M.; Zehnder, M.; Rüegger, H.; Pregosin, P. S. *Helv. Chim. Acta* **1995**, *78*, 265.

(5) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. For a leading reference, see: Sawamura, M.; Nakayama, Y.; Tang, W.-M.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 9090.

(6) Trost, B. M. *Acc. Chem. Res.* **1996**, *29*, 355.

(7) Trost, B. M.; Breit, B.; Organ, M. G. *Tetrahedron Lett.* **1994**, *35*, 5817.

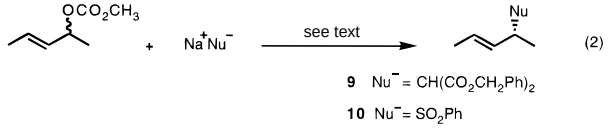
(8) Bunt, R. C., Ph.D. Thesis, Stanford University, 1995.

(9) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089.

(10) Sasaki, T.; Lieberman, M. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNirol, D. D., Vögtle, F., Lehn, J. M., Murakami, Y., Eds.; Pergamon Press: Oxford, 1996; Vol. 4, Chapter 5. Landini, D.; Maia, A.; Penso, M. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNirol, D. D., Vögtle, F., Lehn, J. M., Gokel, G. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 1, Chapter 11. Lehn, J. M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, 1995; Chapter 8.4. Pregel, M. J.; Jullien, L.; Lehn, J. M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1637.

S0002-7863(97)00686-0 CCC: $14.00

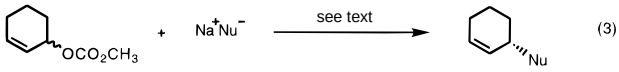
lysts. Performing reaction 1 with a catalyst derived from 0.2 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$ and 0.6 mol % **3** with dibenzyl sodiomalonate in methylene chloride at 40 °C gave a 90% yield of alkylated product of 96% ee as determined by chiral HPLC.[11] A similar reaction differing only in maintaining room temperature with the dipod ligand **4** in the normally difficult acyclic case (eq 2)[12] gave a 68% yield of product **9** of 90% ee. Using sodium benzenesulfinate as the nucleophile and $(dba)_3Pd_2{\cdot}CHCl_3$ (dba = dibenzylideneacetone) as the palladium source in an aqueous methylene chloride two phase system gave an 81% yield of **10** of >99% ee.



9 $Nu^- = CH(CO_2CH_2Ph)_2$

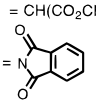
10 $Nu^- = SO_2Ph$

Our earlier studies suggested that the cation effect leading to high ee derived at least in part from a slower rate of alkylation which permitted equilibration of the intermediate π-allylpalladium complex so that it effectively symmetrized.[13] On the other hand, these reactions with ligands **3** and **4** appear to show significant rate enhancements and still high ee. For example, the time for complete consumption of starting material for the cyclohexenyl substrate as shown in eq 3 dropped from 16 h at 40 °C with the malonate nucleophile using the standard ligand **1** to only 2 h with the tetrapod ligand **3** (99% yield, 99% ee).



11 $Nu = CH(CO_2CH_2Ph)_2$

12 Nu =



13 $Nu = SO_2Ph$

With sodium phthalimide as nucleophile, the standard ligand required tetrahexylammonium bromide as a phase transfer catalyst in an aqueous methylene chloride two-phase system and led to completion after 18 h with 5 mol % catalyst. The dipod ligand required no phase transfer agent, went to completion in 2 h with only 0.25 mol % catalyst, and provided **12** of 98% ee in 91% yield.

The reaction of the cyclohexenyl substrate with sodium benzenesulfinate to give **13**[14] was explored in greater depth. For these studies, the reaction conditions involved 0.13 mol % $(dba)_3Pd_2{\cdot}CHCl_3$ and 0.30 mol % ligand in a water/methylene chloride two-phase mixture at 0 °C. A significant rate enhancement was observed for the dipod ligand **4** compared to the standard ligand **1** wherein 50% conversion occurred in less than 10 min in the former and less than 15% conversion occurred even after 180 min in the latter. Furthermore, addition of 0.30 mol % 15-crown-5 with the standard ligand **3** saw the conversion increase only to 40% after 180 min. As might be anticipated for an ion channel effect, there is a dependence on the cation as shown in Figure 1. Comparison of the times to reach 50% conversion with the dipole ligand **4** showed a strong selectivity for Na^+ (<10 min) compared to Li^+ (70 min), K^+ (180 min),

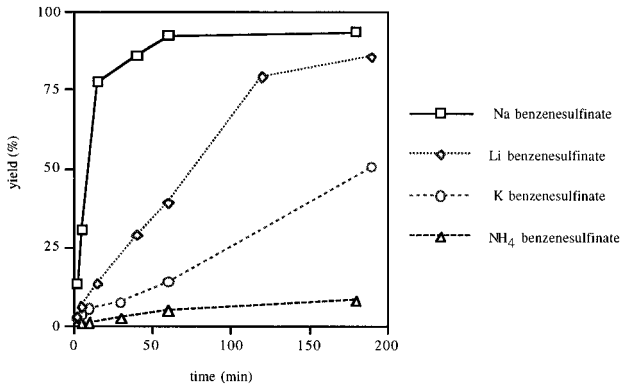


Figure 1. Cation effect with dipodal ligand **4**.

or NH_4^+ (>180 min). The tetrapodal ligand **3** shows similar behavior to the dipodal ligand **4**.

The dipodal and tetrapodal ligands **4** and **3** show that sodium salts can give excellent ee values and simultaneously effect a rate enhancement in contrast to our earlier studies with ligand **1**. Furthermore, while the rate is cation dependent, the ee became cation independent, being high in all cases. A consistent explanation takes into account the dynamic structure that this "chiral pocket" appears to exhibit, especially with the five-membered ring substrate. By incorporating arms into the "pocket," either the relaxation of the "pocket" to provide the symmetry necessary for high chiral recognition is enhanced or the "pocket" already possesses the structure required for high enantioselectivity. In either case, speeding up the rate of the alkylation need not have a significant influence on the ee. The enhanced rate undoubtedly derives from the metal binding effect which would make the anion freer and thus more nucleophilic as in polyethers. The cation specificity attests to this conclusion. It is remarkable that simple unstructured glyme-like units show such specific effects and that the more highly organized crown structures are not required.[15,16] Hayashi and Ito et al.[5,17] have developed a family of ligands wherein asymmetric interaction of an arm directly with the incoming nucleophile is responsible for molecular recognition. The fact that both the symmetrical tetrapod and the unsymmetrical dipod ligands **3** and **4** gave the same results suggests that such an asymmetric interaction with the incoming nucleophile is not responsible for the molecular recognition. Thus, it appears reasonable to conclude that in this family of ligands, secondary interactions affect transport of the nucleophile but not molecular recognition. The results support the contention that molecular sculpting of the "chiral pocket" in a somewhat rational fashion to elicit specific selectivities may be possible and readily realized experimentally by the strategy outlined herein.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health, General Medical Sciences, for their generous support of our programs. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Characterization data and experimental procedures for **3**−**8**, summary table, and figure depicting rate comparisons between standard and dipod ligands (9 pages). See any current masthed page for ordering and Internet access instructions.

JA9706864

(11) Chiralpak AD column eluting with 90:10 heptane/2-propanol was employed.

(12) Cf: Trost, B. M.; Krueger, A. C.; Bunt, R. C.; Zambrano, J. *J. Am. Chem. Soc.* **1996**, *118*, 6520.

(13) Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1996**, *118*, 235.

(14) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662.

(15) For a review, see: Gokel, G. W.; Murillo, O. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNirol, D. D., Vögtle, F., Lehn, J. M., Gokel, G. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 1, Chapter 1.

(16) Cf.: Zaugg, H. E.; Ratajczyk, J. F.; Leonard, J. F.; Schaefer, A. D. *J. Org. Chem.* **1972**, *37*, 2249.

(17) Hayashi, T. *Pure Appl. Chem.* **1988**, *60*, 7.